REMARKS/ARGUMENTS

Status of the Claims

Claims 1-6 and 10-15 are under examination. Claims 7-9 and 16-37 are cancelled. Claims 1, 5, 6, 10, 11 have been amended.

Rejection of Claims 1-6 and 10 are rejected under 35 U.S.C. §102(e)

Claims 1-6 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication 2003/0068312 (McCarthy), filed October 4, 2001 (of record).

Claims 1-6

Claims 1-6 are drawn to an isolated nucleic acid molecule comprising a nucleotide sequence encoding a cynomolgus monkey Dickkopf-4 (cDkk-4) protein which has an amino acid sequence as set forth in SEQ ID NO:2 (claims 1-4), wherein the nucleic acid has a nucleotide sequence as set forth in SEQ ID NO: 1 (claim 5) and to an isolated protein comprising an amino acid sequence as set forth in SEQ ID NO:2 (claim 6).

The outstanding anticipation rejection is premised on the position that the limitations "*a* nucleotide sequence" (claims 1 and 5) or "*an* amino acid sequence" (claims 1 and 6) can be met by the occurrence of as few as two consecutive nucleotides, or amino acids, that are identical to the reference sequences.

The Office Action indicates that US Patent Application Publication No.: 2003/0068312 (McCarthy) discloses a nucleic acid sequences set forth SEQ ID NO:4 which is 94.5% identical to SEQ ID NO:1 of the claims as demonstrated by an alignment included in the Office Action. Based on the information provided by the alignment it is concluded that the prior art sequence "contains multiple occurrences of 'a nucleotide sequence as set forth in SEQ ID NO:1' as recited in the instant claims."

The Office Action further indicates that US 2003/0068312 also discloses SEQ ID NO:5, a polypeptide which is 95.5% identical to SEQ ID NO:2, as shown by a second alignment included in the Office Action.

Based on these observations, the Examiner concludes that the prior art sequence contains multiple occurrences of "an amino acid sequence as set forth in SEQ ID NO:2" as recited in the instant claims.

The Office Action indicates that this rejection could be overcome by amending the indefiniteness articles "a" and "an" to "the" in claims 1, 5 and 6.

Claims 1, 5 and 6 have been amended in accordance with the Examiner's suggestion. As amended, claim 1 reads:

> An isolated nucleic acid molecule comprising a nucleotide sequence encoding a cynomolgus monkey Dickkopf-4 (cDkk-4) protein comprising *the* amino acid sequence as set forth in SEQ ID NO:2.

As amended claim 5 reads:

> The isolated nucleic acid of Claim 1 wherein the nucleic acid has *the* nucleotide sequence as set forth in SEQ ID NO:1.

As amended claim 6 reads:

> An isolated protein comprising *the* amino acid sequence as set forth in SEQ ID NO:2.

Neither of the cited prior art references discloses a nucleic acid sequence comprising the nucleotide sequence set forth in SEQ ID NO:1, or a cynomolgus monkey Dickkopf-4 (cDkk-4) protein comprising the amino acid sequence set forth in SEQ ID NO:2. This statement is corroborated by the sequence alignments provided in the Office Action which establish that US Patent Application Publication No.: 2003/0068312 (McCarthy) discloses a nucleic acid sequences set forth SEQ ID NO:4 which is 94.5% identical to SEQ ID NO:1, and a polypeptide which is 95.5% identical to SEQ ID NO:2. Accordingly, the cited references do not deprive the subject matter of the claims under examination of their novelty.

In light of the above-described amendments and reasoning Applicants respectfully request reconsideration and withdrawal of the outstanding rejection of Claim 13 under 35 U.S.C.§102(e).

Claim 10

Claim 10 is drawn to a method for producing a cynomolgus monkey Dickkopf-4. As "cynomolgus monkey Dickkopf-4" is not recited in the claim to comprise the sequence set forth in SEQ ID NO:2, the structural scope of this term must be found in the specification, which, in turn, states that the cDkk-4 protein of the invention has an amino acid sequence as set forth in SEQ ID NO:2 (paragraph [0017] in the published application). As noted above, this definition does not exclude the polypeptide of SEQ ID NO:5 in McCarthy. McCarthy teaches production of the disclosed polypeptide by recombinant expression, thereby allegedly anticipating the method of instant claim 10.

The Office Action indicates that this rejection could be overcome by reciting the amino acid sequence set forth in SEQ ID NO:2 in claim 10.

Claim 10 has been amended in accordance with the Examiner's suggestion. As amended, claim 10 reads:

> A method for producing a cynomolgus monkey Dickkopf-4 (cDkk-4) protein *comprising the amino acid sequence as set forth in SEQ ID NO:2* which binds a low-density lipoprotein receptor protein 5 (LRP5) comprising:
>
> (a) providing a nucleic acid encoding the cDkk-4 protein operably linked to a heterologous promoter;
>
> (b) introducing the nucleic acid into a cell to produce a recombinant cell; and
>
> (c) culturing the recombinant cell under conditions which allows expression of the cDkk-4 protein to produce the cDkk-4.

In light of the above-described amendment which introduces the requirement that the cDKK-4 comprise the amino acid sequence set as set forth in SEQ ID NO:2, which excludes the polypeptide of SEQ ID NO:5 disclosed in McCarthy, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection of Claim 13 under 35 U.S.C.§102(e).

Claims 11, 12, 14 and 15

Claims 11, 12, 14 and 15 are rejected under 35 U.S.C. §102(e) as being anticipated by US Patent Application 20040038860 (Allen), filed May 17, 2002.

The instant claims are drawn to a method wherein the ability of an anylate to decrease binding of Cynomolgus monkey Dickkopf-4 to a Dkk-4 receptor is determined as an indication of whether the analyte is an antagonist of Dickkopf-4.

The Office Action reiterates the point that because the generic recitation of "cynomolgus monkey Dickkopf-4" does not distinguish the claimed polypeptide from Dkk-4 polypeptides in the prior art. The Office Action notes that Allen teaches that "Dkk proteins" includes Dkk-4.

Allen teaches a method for identifying compounds which modulate Dkk and LRP5/LRP6/HBM interactions. The prior art method comprises use of a Dkk fusion protein comprising a fluorescent tag, as recited in instant claim 14 and 15. The "[m]ethod taught by Allen relies on Resonance Energy Transfer and thus would detect a reduction in binding (as instantly claimed), as well as more subtle disruptions in molecular interaction.

Claim 11 has been amended to more clearly define the structural scope of the claim in a manner which distinguishes the claimed cDkk-4 polypeptide from the prior art sequences. As amended, Claim 11 reads:

> A method for determining whether an analyte is an antagonist of Dickkopf 4 (Dkk-4) comprising:
> (a) providing a polypeptide comprising the extracellular domain of a Dkk-4 receptor;
> (b) contacting the polypeptide with a cynomolgus monkey Dkk-4 (cDkk-4) *protein comprising the amino acid sequence as set forth in SEQ ID NO:2* and the analyte; and
> (c) determining whether binding of the cDkk-4 to the polypeptide is decreased in the presence of the analyte, wherein a decrease in the binding indicates that the analyte is an cDkk-4 antagonist.

In light of the above-described amendment which introduces the requirement that the cDKK-4 comprise the amino acid sequence set as set forth in SEQ ID NO:2,

Applicants respectfully request reconsideration and withdrawal of the outstanding rejection of Claim 13 under 35 U.S.C.§102(e).

Rejection of Claim 13 under 35 U.S.C. §103(a)

Claim 13 is rejected under 35 U.S.C. §103(a) as being unpatentable over US Application Publication 20040038860 (Allen) as applied to claims 11, 12, 14 and 15 above and further in view of Mao *et al.*, Nature 417:664-667 (2002) (of record). As noted, Allen teaches a method for identifying compounds which modulate Dkk and LRP5/LRP6/HBM interactions, which anticipates the general methods of instant claim 11.

Allen does not teach, however, an embodiment of the method wherein the Dkk receptor is kremen1 or kremen2, as required by instant claim 13. Neither the prior art nor the instant specification provides a direct demonstration that kremen proteins are receptors for Dkk-4.

Mao *et al.,* teach that kremen proteins are receptors for Dkk-1 and Dkk-2. Claim 13 relies on the expectation that Dkk-4 will act in a similar fashion to the characterized Dkk proteins and that kremen proteins will perform in a binding assay in a manner similar to LRP5/6. The Office Action concludes that the expectation of success is high, based on the statement that if it were not, the claim would not be enabled by the specification. More specifically, the Office Action states that "the use of kremen instead of LRP5/6 in a method similar to that taught by Allen, is an example of choosing from a finite number of solutions with a reasonable expectation of success" (Office Action, page 7). The Office Action concludes that it would be prima facie obvious for one of skill in the art to modify the assay as taught by Allen by using kremen proteins instead of LRP5/6 to arrive at the method of claim 13.

Prior to the Mao *et al* publication it was known that Dkk1 inhibits Wnt signaling by binding to and antagonizing LRP5/6. The cited publication establishes that the transmembrane proteins Kremen1 and Kremen2 are high-affinity Dkk1 receptors that functionally cooperate with Dkk1 to block Wnt/beta-catenin signaling. The disclosure teaches that Kremen2 forms a ternary complex with Dkk1 and LRP6, and induces rapid endocytosis and removal of the Wnt receptor LRP6 from the plasma membrane. The

results indicate that Kremen1 and Kremen2 are components of a membrane complex modulating Dkk1-mediated Wnt signaling through LRP6 in vertebrates.

As amended the method of claim 13 (which depends from base claim 11) requires the use of a cynomolgus monkey Dkk-4 (cDkk-4) protein comprising the amino acid sequence as set forth in SEQ ID NO:2. Prior to the instant disclosure the amino acid sequence of cDkk-4 was not known, therefore a skilled artisan would not have been in a position to practice the method of claims 11 or 13. Furthermore, without knowledge of the cDkk-4 protein there was no motivation to practice the method of Allen (use of LRP5/6), or to modify the method of Allen by using Kremen proteins instead of LRP5/6 in order to determine whether an analyte is an antagonist of Dickkopf 4 (Dkk-4). Accordingly, the cited references do not render the subject matter of the instant claims obvious.

In light of the above-described amendments and reasoning Applicants respectfully request reconsideration and withdrawal of the outstanding rejection of Claim 13 under 35 U.S.C.
§103(a).

CONCLUSION

In light of the claim amendments and remarks set forth above Applicants are of the opinion that the claims of this application particularly point out and distinctly claim the subject matter of a patentable invention. Therefore, Applicants respectfully solicit the Examiner to expedite prosecution of the patent application to issuance. Should the Examiner have any question, he is encouraged to telephone the undersigned.

Respectfully submitted,

By _____

Patricia Chisholm
Reg. No. 45,822
Assistant Counsel

MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-5738